Deutsche Gesellschaft für Nuklearmedizin e.V.

SUMMER SCHOOL 2015

Translational Research in Molecular Imaging and Radionuclid Therapy

August 25 - 27, 2016

Oncology

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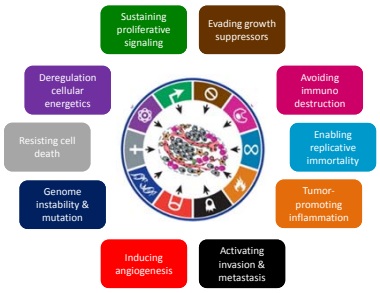
Klinik für Nuklearmedizin,
Universitätsklinikum Aachen

Oncology
Hallmarks of Cancer as diagnostic and therapeutic Targets



Hanahan et al. Cell 2011

Oncology
Hallmarks of Cancer as diagnostic and therapeutic Targets

Hanahan et al. Cell 2000

A higher metabolic rate increases mutations rates and contributes to cancer development!

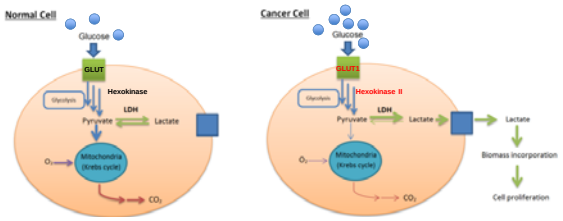
Shuttlerstock; Beshon et al. 2015

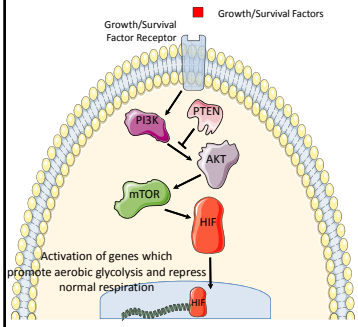
Oncology
Reprogramming Energy Metabolism as „core“ hallmark capability of cancer cells

Deregulation cellular energetics

Switch in cancer cells towards increased metabolic rate of:

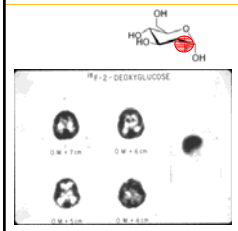
- glucose
- amino acids
- lipids



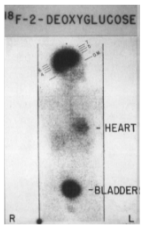


Mechanism beyond the metabolic switch:

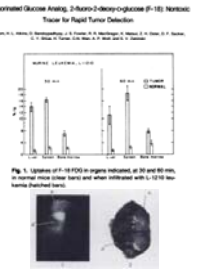
- Growth or survival factor signaling activates the PI3K signaling pathway.
- Activated PI3K activates AKT, which then activates mTOR, which then activates HIF.
- HIF moves into the nucleus of the cell and activates genes that promote aerobic glycolysis while repressing normal metabolism.
- Activated PI3K can be attenuated by tumor suppressor protein PTEN.



First whole-brain (planar) and tomographic FDG images of brain function of a normal volunteer (1976; Reivich M. et al.)

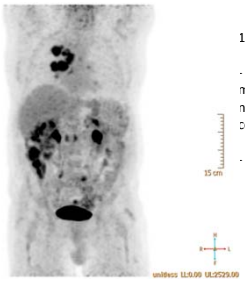


First whole body FDG images of a normal volunteer (1976; Reivich M. et al.)



J Nucl Med 21: 670–675, 1980

^{18}F-FDG PET/CT



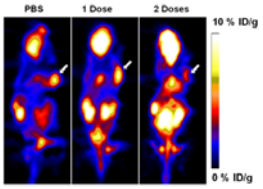
18F-FDG PET/CT in **clinical** routine:

- staging and restaging of a variety of malignant tumors, including lymphoma, melanoma, non–small cell lung cancer, esophageal cancer, and colorectal cancer
- monitoring tumor response to therapy

^{18}F-FDG PET/CT

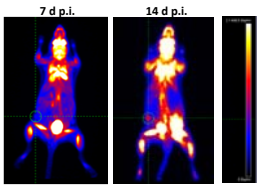
18F-FDG PET/CT in **pre-clinical** routine:

- evaluation of tumor growth *in vivo*
- monitoring tumor response to therapy



Representative decay-corrected whole-body coronal microPET images of mice bearing UM-SCC-22B tumors at 1 h after intravenous injection of ^{18}F-FDG (1.85 MBq/mouse) **after Doxil** or PBS treatment.

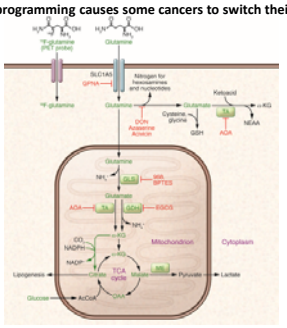
Zhang et al. Theranostics 2011



Representative decay-corrected whole-body coronal microPET images of mice bearing MDA-MB 231 tumors at 0.5h after intravenous injection of ^{18}F-FDG (1.5 MBq/mouse) **7 and 14 days after xenotransplantation**.

Morgenroth et al. unpublished data

Metabolic reprogramming causes some cancers to switch their energy source from glucose to glutamine…



Rationale for glutamine as an alternative energy source:

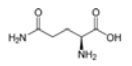
- highest concentration (0.5–1 mM) among all of the amino acids circulating in the blood

- during period of rapid growth or stress increased demand for glutamine supply

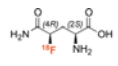
- contributes to both of energy forming pathways in cancer cells: oxidative phosphorylation and glycolysis

Hensley et al. J Clin Invest 2013

glutamine

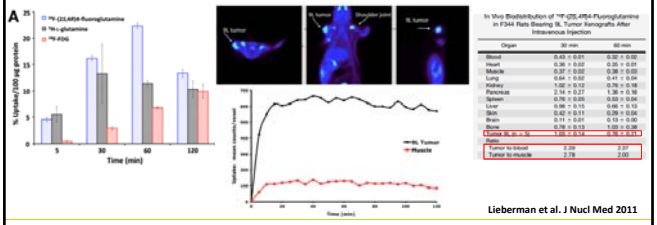


[18F](2S,4R)4-fluoroglutamine
(2S,4R)4-FGln



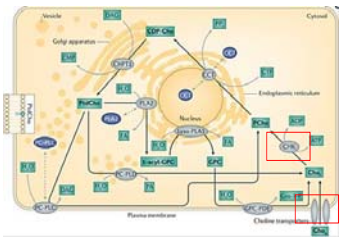
Development of glutamine-derivatives as PET tracer for:

- molecular imaging of FDG-negative glutamine-addicted tumors (neuroblastoma)
- identification of patients responding to inhibitors of glutamine metabolism (therapy planning)



Lieberman et al. J Nucl Med 2011

The fat side of cancer:
Increased de novo synthesis of fatty acids as source of energy, constituents for cell membrane and modification of proteins.

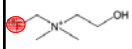


Choline as target for molecular imaging of cancer:

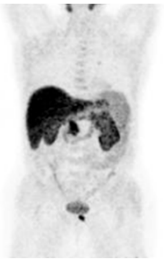
- Enhanced choline uptake and intracellular turnover of phosphatidylcholine in many malignant tumors (prostate, breast, ovarian) due to overexpression of choline transporter and choline kinase

Glunde et al. Neture Rev 2011

Oncology
Metabolic switch: one hallmark many faces



^{18}F-Choline PET/CT

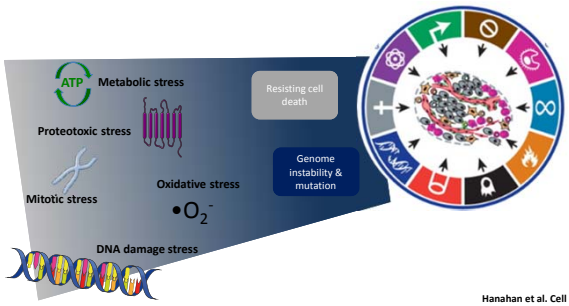


18F-Cholin PET/CT in **clinical** routine:

- diagnosis and staging of patients with primary prostate cancer

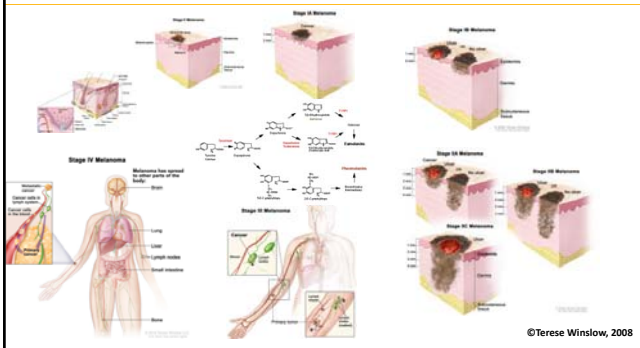
- monitoring tumor response to therapy

Oncology
Hallmarks of Cancer as diagnostic and therapeutic Targets



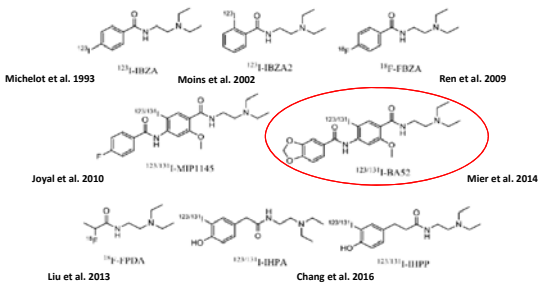
Hanahan et al. Cell 2011

Oncology
Melanin as druggable therapeutic target



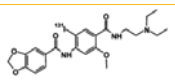
©Terese Winslow, 2008

Oncology
Melanin as druggable therapeutic target



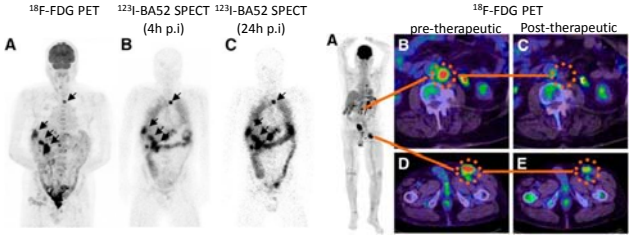
Michelot et al. 1993
Moins et al. 2002
Ren et al. 2009
Joyal et al. 2010
Mier et al. 2014
Liu et al. 2013
Chang et al. 2016

Oncology
Melanin as druggable therapeutic target



Radiopharmaceutical Therapy of Patients with Metastasized Melanoma with the Melanin-Binding Benzamide ^{131}I-BA52

Mier et al. J Nucl Med 2014



Oncology
Chronic cell proliferation: most fundamental trait of cancer cells

Sustaining proliferative signaling

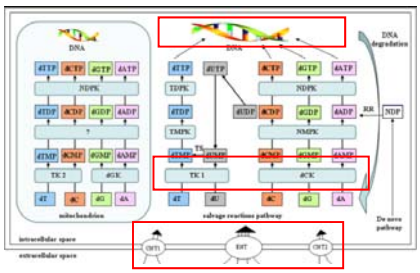
Evading growth suppressors

Cancer cells acquire the capability to sustain proliferative signaling:

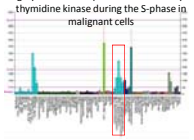
- by increased production of growth factors e.g. EGF, IGF-1 (autonomous growth)
- by overexpression of cognate receptors e.g. EGFR, IGF-1R (hypersensitivity)
- by somatic mutations of signaling pathways operating downstream of growth receptors e.g. B-Raf, PI3-K (constitutive activation)
- by disruption of regulatory negative-feedback mechanism and inactivation of growth suppressors e.g RB protein, TP53 (uncontrolled proliferation)

Oncology
Chronic cell proliferation: most fundamental trait of cancer cells

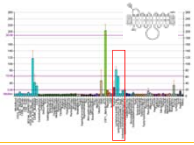
Sustained and continued demand on supply of DNA building blocks as tumor specific target



Highly increased expression and activity of thymidine kinase during the S-phase in malignant cells

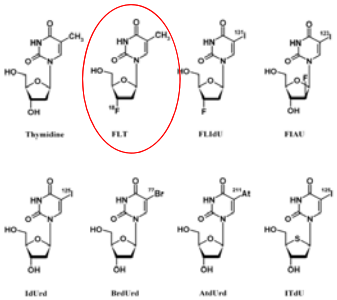


Highly increased expression of nucleoside transporter hENT1 in malignant cells

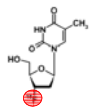


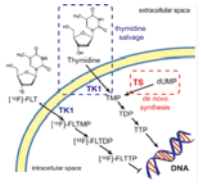
Oncology
Chronic cell proliferation: most fundamental trait of cancer cells

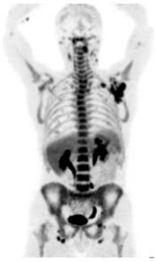
Nucleoside analogues for molecular imaging and therapy of cancer



^{18}F-FLT PET/CT

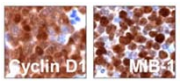






18F-FLT PET/CT in **clinical** routine:

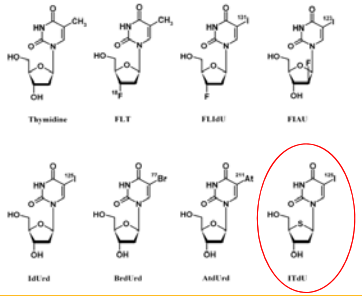
- diagnosis and staging of a variety of malignant tumors
- monitoring tumor response to therapy



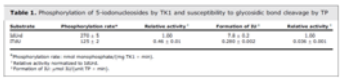
McKinley et al. PLOS ONE 2013

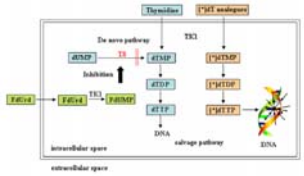
Herrmann et al. J Nucl Med 2011

Nucleoside analogues for molecular imaging and therapy of cancer



Preclinical evaluation of nucleoside analogue ITdU for endogenous therapy





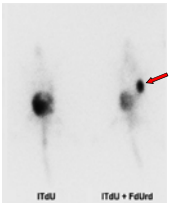
Morgenroth et al. Clin Cancer Res 2008

Biochemical features of ITdU (5-iodo-4´-thio-2-desoxyuridin):

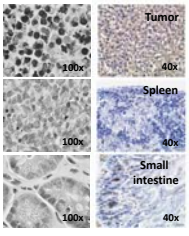
- phosphorylated by thymidine kinase 1
- no enzymatic degradation by thymidine phosphorylase
- 5-Fluor-2´-desoxyuridin (FdUrd) -dependent cell uptake and incorporation into DNA of proliferating tumor cells
- DNA-incorporated [125I]ITdU induces efficiently apoptosis in more than 90% of tumor cells causing extensive tissue damage

Preclinical evaluation of nucleoside analogue $^{123/125}$I-ITdU for endogenous therapy

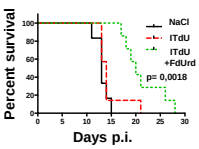
SPECT 24h p.i. of ^{123}I-ITDU



Microautoradiography and TUNEL analysis 24h p.i. of ^{125}I-ITDU



Survival curve (single application of ^{125}I-ITDU)



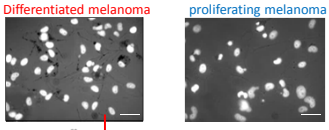
Morgenroth et al. Clin Cancer Res 2008

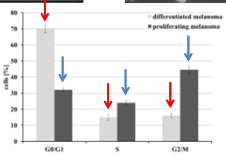
Oncology
Chronic cell proliferation: most fundamental trait of cancer cells

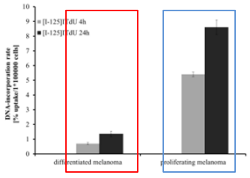
***In vivo* Switching of Human Melanoma Cells between Proliferative and Invasive States**

Hoek et al. Cancer Res 2008

Differentiated melanoma | proliferating melanoma

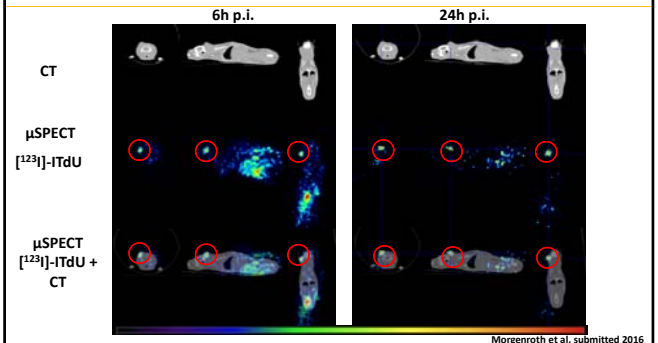






Morgenroth et al. submitted 2016

Oncology
Chronic cell proliferation: most fundamental trait of cancer cells

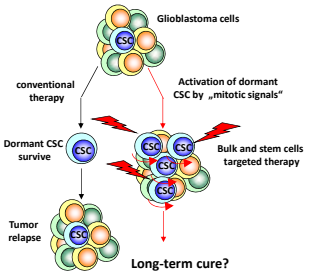


Morgenroth et al. submitted 2016

Oncology
Cancer stem cells – a new target for ITdU

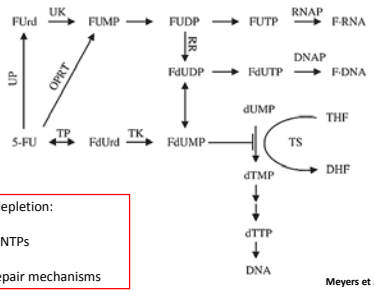
Unique properties of stem cells

- Dormancy
- high mitotic activity (inducible in response to „injury-signals")
- asymmetric division:
  - Self-renewal
  - Differentiation potential
- active signaling pathways essential for maintenance of „self-renewal" capacity like Hedgehog (Hh), Wnt und Notch
- resistance to drugs and toxins through expression of several ABC transporters and scavenger systems, an active DNA-repair capacity and resistance to apoptosis



Oncology
Cancer stem cells – targeting by induction of differentiation

Inhibition of *de novo* thymidine synthesis by FdUrd

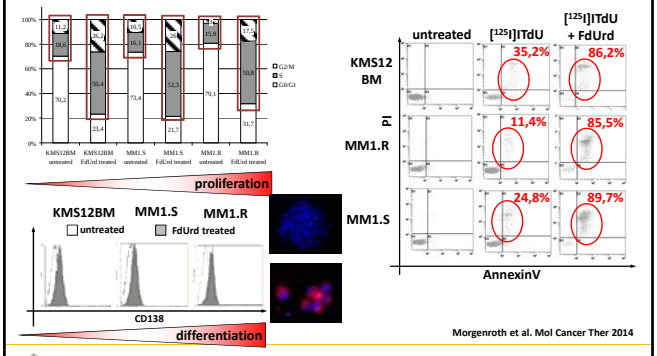


Consequence of dTTP pool depletion:

- Intracellular imbalance in dNTPs
- Loss of potential for DNA repair mechanisms

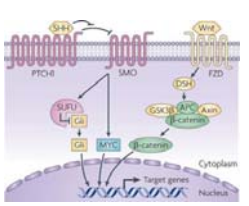
Meyers et al. Oncogene 2003

Oncology
Myloma stem cells – targeting by induction of proliferation and differentiation



Morgenroth et al. Mol Cancer Ther 2014

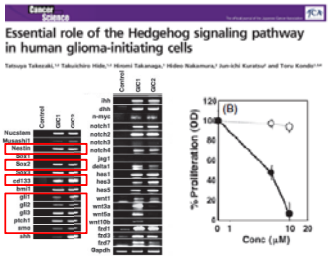
Oncology
Glioblastoma stem cells – targeting of the self-renewal signaling pathway



Huse et al. Nature Rev 2010

Report

HEDGEHOG-GLI1 Signaling Regulates Human Glioma Growth, Cancer Stem Cell Self-Renewal, and Tumorigenicity



Takezaki et al. Cancer Sci 2011

Oncology
Glioblastoma stem cells – targeting of the self-renewal signaling pathway

Proliferation Induction of dormant TSC by Stimulation of Hh Pathway with the Sonic Hedgehog Ligand Shh

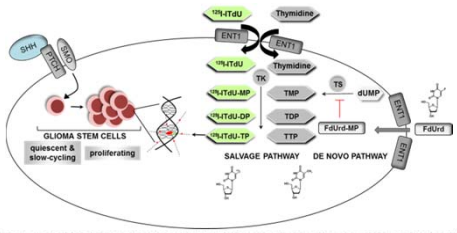
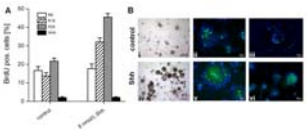


Figure 6: A two-step killing strategy of glioblastoma multiforme stem cells. Glioma stem cells are activated by HH signaling pathway to enter mitosis. The proliferating glioma stem cells incorporate the radiolabelled thymidine analogue [I-125]ITdU into the DNA via the salvage pathway. This effect is further enhanced by simultaneous FdUrd mediated inhibition of the *de novo* pathway of thymidine synthesis.

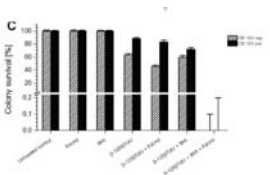
Morgenroth et al. Oncotarget 2014

Oncology
Glioblastoma stem cells – targeting of the self-renewal signaling pathway



Effect of SHH stimulation on proliferation of glioma cells and normal astrocytes. (A) Percentage of BrdU+ R8, R18, R28 cells and normal human astrocytes (NHA) after stimulation with SHH in comparison with unstimulated cells. (B) Phase-contrast images (i, iv) and fluorescent images after staining with BODIPY-Cyclopamine (anti- Smo, green; ii, v) and anti-BrdU antibody (green; iii, vi) of unstimulated and SHH stimulated R28 neurospheres (Hoechst nuclei staining in blue).

Clonogenic survival of $CD133^-$ and $CD133^+$ R28 cells after incubation with [I-125]ITdU in dependency on FdUrd and SHH stimulation.

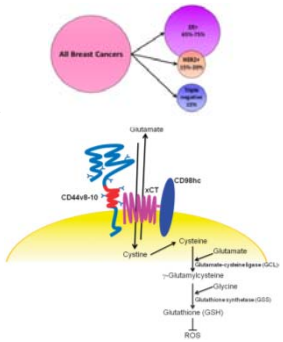


Morgenroth et al. Oncotarget 2014

Oncology
Breast cancer stem cells – targeting of the scavenger system

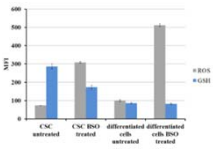
Represents a subtype of breast cancer with unique molecular and clinical characteristics:

- Comprises about 15-25% of all breast cancers
- Lack ER, PR and HER2 – **no targeted therapies**
- exhibits strong phenotypic similarity to **cancer stem cell (CSC)**
- Therapy resistance: elevated GSH concentration



Oncology
Breast cancer stem cells – targeting of the scavenger system

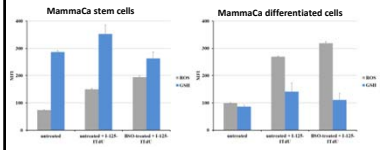
Miran et al. 2016



Antioxidant status (FACS)

- CSC exhibits increased GSH level
- GSH inhibition with BSO decreases GSH and increases ROS level in CSC

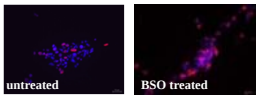
Effect of I-125-ITdU on GSH & ROS level



- Nano-irradiation generates ROS and increases GSH level

GSH mediated radiosensitivity in CSC

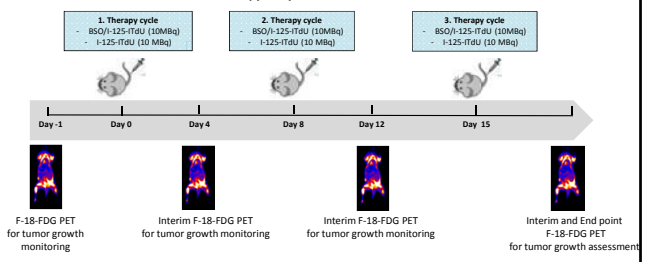
Induction of apoptosis: pHA2X staining



- BSO sensitizes CSC to I-125-ITdU

Oncology
Breast cancer stem cells – targeting of the scavenger system

Therapy study in BreastCa mice



F-18-FDG PET for tumor growth monitoring

Interim F-18-FDG PET for tumor growth monitoring

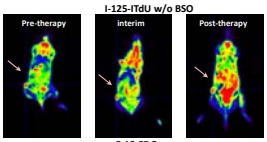
Interim F-18-FDG PET for tumor growth monitoring

Interim and End point F-18-FDG PET for tumor growth assessment

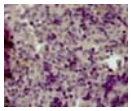
Miran et al. 2016

Oncology
Breast cancer stem cells – targeting of the scavenger system

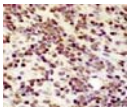
F-18-FDG scans
I-125-ITdU w/o BSO



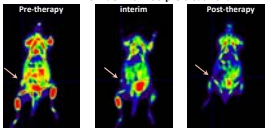
TUNEL Assay
I-125-ITdU w/o BSO



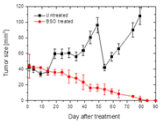
TUNEL Assay
I-125-ITdU with
BSO pre-treatment



F-18-FDG scans
I-125-ITdU with BSO pre-treatment



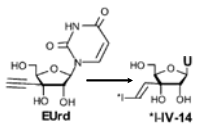
Tumor growth in I-125-ITdU treated animals (-/+BSO)



Miran et al. 2016

Preclinical evaluation of nucleoside analogue 3'-(E)-(2-Iodovinyl)uridin (IV-14)

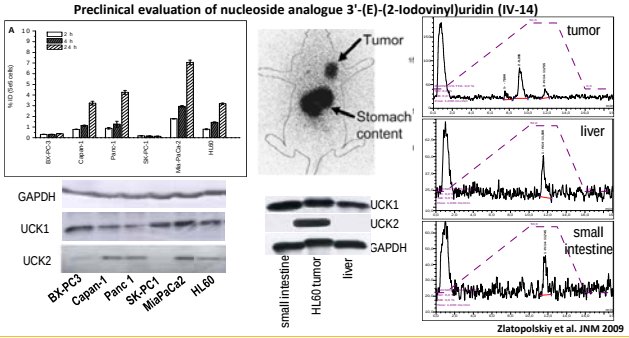
EUrd $\xrightarrow{UCK2}$ EUrdMP ⟶ EUrdDP ⟶ EUrdTP ⟶ **inhibition of RNA synthesis**



Rationale for development of RNA-addressing nucleoside analogues

- for targeting of tumors with low mitotic index
- RNA-synthesis not S-phase restricted
- Uridine Cytidine Kinase 2 (UCK2) highly overexpressed in pancreas, colon, breast, lung, and ovarian tumor tissues

Preclinical evaluation of nucleoside analogue 3'-(E)-(2-Iodovinyl)uridin (IV-14)



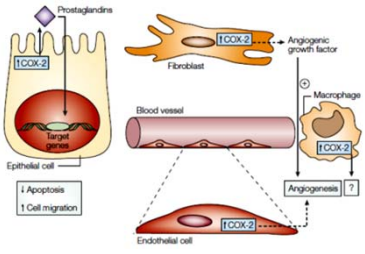
Zlatopolskiy et al. JNM 2009

Tumor-promoting inflammation

- Chronic infection and inflammation cause cancer in several organs including the colon, liver and large intestine.
- Tumor-promoting inflammatory cells (macrophages, mast cells, neutrophils, T- and B-cells) release signaling molecules (e.g. EGF, VEGF, FGF2, chemokines, cytokines) and pro-invasive matrix-degrading enzymes (MMP-9).
- Inflammatory cells (macrophages) release reactive oxygen species that are actively mutagenic for nearby cancer cells.

Tumor-infiltrating inflammatory cells induce and support tumor angiogenesis, proliferation of malignant cells, and facilitate tissue invasion.

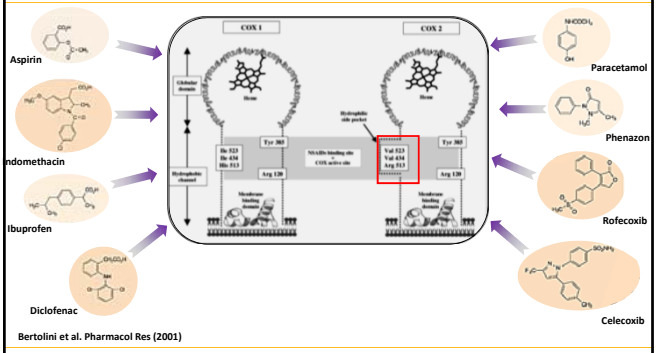
Tumor promoting function in carcinogenesis of cyclooxygenase-2 (COX-2)



Tumorigenesis supporting mechanisms

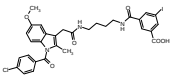
- COX-2 produced prostaglandins cause resistance to apoptosis and enhance cell migration in cancer cells (cell-autonomous effect)
- COX-2 induces production of pro-angiogenic growth factors in fibroblasts and supports migration of endothelial cells (neovascularization)

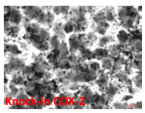
Gupta et al. Nature Rev 2001

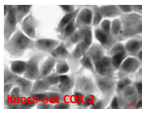


Bertolini et al. Pharmacol Res (2001)

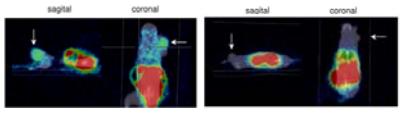
Pre-clinical evaluation of Indomethacin-Derivatives as PET/SPECT tracer for molecular imaging of colorectal carcinoma

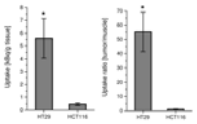






HT29 Xenograft (COX-2$^+$) HCT-116 Xenograft (COX-2$^-$)





Morgenroth et al. submitted 2016